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# Efficient mRNA delivery with graphene oxide-polyethylenimine for generation of footprint-free human induced pluripotent stem cells

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## Abstract

Clinical applications of induced pluripotent stem cells (iPSCs) require development of technologies for the production of "footprint-free" (gene integration-free) iPSCs, which avoid the potential risk of insertional mutagenesis in humans. Previously, several studies have shown that mRNA transfer can generate "footprint-free" iPSCs, but these studies did not use a delivery vehicle and thus repetitive daily transfection was required because of mRNA degradation. Here, we report an mRNA delivery system employing graphene oxide (GO)-polyethylenimine (PEI) complexes for the efficient generation of "footprint-free" iPSCs. GO-PEI complexes were found to be very effective for loading mRNA of reprogramming transcription factors and protection from mRNA degradation by RNase. Dynamic suspension cultures of GO-PEI/RNA complexes-treated cells dramatically increased the reprogramming efficiency and successfully generated rat and human iPSCs from adult adipose tissue-derived fibroblasts without repetitive daily transfection. The iPSCs showed all the hallmarks of pluripotent stem cells including expression of pluripotency genes, epigenetic reprogramming, and differentiation into the three germ layers. These results demonstrate that mRNA delivery using GO-PEI-RNA complexes can efficiently generate "footprint-free" iPSCs, which may advance the translation of iPSC technology into the clinical settings.

**Keywords:** Footprint-free transgene-free; Gene delivery; Graphene oxide-polyethylenimine complex; Human induced pluripotent stem cells; Integration-free; RNA delivery; iPSC.



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